STUDIES UPON THE CEREBRAL CORTEX IN THE NORMAL HUMAN BRAIN AND IN DEMENTIA PARALYTICA.[1]

By G. Alfred Lawrence, M.D., Ph.D., of New York.

INSTRUCTOR IN DISEASES OF THE MIND AND NERVOUS SYSTEM, NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL

Introductory. The following contribution to the study of the cerebral cortex in the normal human brain as compared to that in dementia paralytica, does not include much that is new to the pathology of the latter, but aims to present the subject in a somewhat different manner than has heretofore been done. The writer's perusal of many anatomical and pathological articles has often been unsatisfactory to himself, owing to many generalized statements of conditions found without any adequate illustrations of what was really to be seen. It has been the endeavor in this article to present and describe photomicrographs of actual sections from a practically normal human brain histologically by way of comparison, and to follow these by photomicrographs of sections of a brain of a well marked case of dementia paralytica. These photomicrographs have been supplemented by drawings. The possibilities as well as the limitations of photomicrography in preparations stained by the Nissl method, it seems to the writer, are fairly well brought out in this article, and this was one of the objects sought in its presentation. That photomicrographs show structure and arrangement in but one plane of limited thickness is true. It is also true, however, that they show exactly what is there and the exact relation to other parts, and there is no personal equation such as is bound to occur in any drawing. A drawing, on the other hand, is always more or less composite, does not show exact relationship, and involuntarily the point to be illustrated is made to assume undue prominence. In work of this kind artefacts are constantly to be looked for and avoided, and the entire process of preparation, as well as the history of the case, must be also carefully considered before any conclusions should be drawn.

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[1] Submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

When it is considered how extremely thin the human cortex is, 1.5 to 3.5 millimeters; that its exterior surface is estimated at about 200,000 square millimeters; that it is intricately arranged in convolutions of varying size and direction; that it is exposed to injury prior to death, at the autopsy, during transportation, and also in the various manipulations of fixation, imbedding, sectioning, staining, decolorizing and mounting, it can readily be seen how artefacts may result by the time the specimen is prepared for examination. This was forcibly brought to the notice of the writer in the examination of some sections but a short time ago. Owing to a dull microtome knife the nuclei of a number of the cells were completely carried outside of the cell-body and the cell-bodies themselves broken and cracked in places. This was at first regarded as a pathological process until attention was called to the fact of the nuclei all being extruded in the same direction, and the breaks and cracks presenting a ragged and irregular appearance. Even when the greatest care is used there will be a variation in thickness in different sections—one being somewhat thinner and the next correspondingly thicker than actually registered by the microtome, although most carefully imbedded, so that variations in the thickness are also to be considered. Furthermore, in fixation, shrinkage or swelling may occur, the latter being demonstrated by Donaldson (1891), who placed fresh nerves in a solution made up of 2.5 per cent of potassium bichromate, plus one-sixth its volume of 95 per cent alcohol for three weeks. He then washed them for one day in water and placed them in 95 per cent. alcohol for three or four days, and finally in 80 per cent alcohol, using six olfactory bulbs, six olfactory tracts, and three pairs of optic nerves of the sheep. This was exactly the same treatment to which his specimens of human nerves had been subjected. The volume of specimens of olfactory bulbs subjected to this treatment and afterwards placed in 80 per cent alcohol was found to be 5.2 per cent greater than fresh specimens, those of the olfactory tracts 8.8 per cent greater, while the optic nerves showed but 2.6 per cent increase in volume. Imbedding in celloidin did not affect the volume, while some stains, as acid fuchsin, produced no change, whereas Delafield's hematoxylin caused swelling, and thus increase in volume. Hammarburg (195) found by experimenting with small blocks of cortical tissue that by accurate measurements blocks hardened in Müller's fluid for three days showed a volumetric increase of 11.7 per cent. Other blocks hardened in Müller's fluid for three weeks, and then, transferred to alcohol and left in the latter for fourteen days, showed, on the other hand, a shrinkage in volume of 43 per cent. In alcohol, 95 per cent, at the end of twenty-four hours, a shrinkage in volume of 20.5 per cent was observed. This shrinkage is furthermore found to vary with different blocks from the same region of the same brain, and it is found that there is no constant relation between pieces from brains of various grades of hardening. Thus the method of fixation must always be taken into consideration. Again, in staining under exactly similar conditions, one section on a slide will be found more intensely stained than another section on the same slide, or even one part of a section will be found more intensely stained than some other part of the same section.

In the subsequent decolorization still greater variations may occur, for, if carried too far, important structures may be completely decolorized. If carried to the other extreme it is impossible to differentiate the various parts. The only way to avoid either extreme is by repeated examination of the sections under the microscope while the process is being carried on, as under similar circumstances one section in a given time may become much more decolorized than another. In regard to mounting of sections stained by the Nissl method, as all were that have been employed in this article, xylol-damar has given the greatest satisfaction to the writer. With this mounting medium there was no subsequent shrinkage, and thus a resulting exposure of the sections, also no decolorization was to be observed at later periods. In some sections mounted for over three years, no decororization was observed, even after several exposures to the intense light necessary for photomicrographic purposes, and frequent exposures to light in their examination under the microscope. Canada balsam was also used, but in time the sections were found partially or completely decolorized. Benzene-colophonium has a tendency to shrink and crack and thus expose portions of the sections in some cases.

It is desired to emphasize the importance of careful attention to all these details at the beginning of the article, in order to impress upon the reader the necessity of the greatest care and conservatism in the interpretation of any changes found in the specimens under observation, and, furthermore, the *correct* interpretation of the same. Before going on to the main subject of the article, a brief historical review of work in this line will be given.

Historical. The first study of the internal structure of the nerve cells began over fifty years ago when Remak (1841) called attention to a fibrillary structure inside the axis cylinder and cell-body of certain nerve cells. Later, Max Schultz (1872) studied nerve fibers and cells from various parts of the central nervous system of different animals with elaborate descriptions of his findings. He dealt with a description of the fibrillary appearance of the interior of the cell-body largely. This doctrine of the nerve cell was afterwards strongly supported by Boll (1873), Schwalbe (1885), and Ranvier (1878). Opposite views were, however, held by Arndt (1874), and Key and Retzius (1876). Arndt, in 1874, described the structure of the spinal ganglion cells and spoke of the presence in them of different kinds of elementary spherules which varied in size and general appearance. Key and Retzius stated that the ground substance of the spinal ganglion cells was homogeneous, but that in it numerous strongly refractive, round, oval granules were present, and they thought the appearance of a concentric striation or fibrillation could be simulated through the arrangement of the granules in rows. Flemming (1882) saw granules within the cells which would stain with nuclear and azo dyes and hematoxylin, but nevertheless affirmed a fibrillary structure of the central cells and of a tortuous or much curved threadwork within the spinal ganglion cells between the granules. In recently published articles (1896) he still maintains that fibrils exist inside the nerve cell protoplasm.

Dogiel (1893) has also expressed himself in favor of the views of a fibrillary structure for certain at least of the nerve cells. In 1885 Nissl published the first of a series of articles in which he calls particular attention, in tissues hardened in alcohol and stained in basic aniline such as majenta red and methylene blue, to certain structures. By Nissl's method these are brought especially well into view, and their arrangement in the protoplasm and their significance for the function of the cell can be studied.

These structures had been previously observed by Flemming and Benda (1882), but by less perfect methods. Nissl at first stained tissues hardened in alcohol with magenta red or methylene blue, and cleared in oil of origanum. This has been modified in several ways, so that at present his treatment is as follows: Small blocks of tissue are hardened in 96 per cent alcohol and fastened by Weigert's method with gum arabic, without imbedding. The sections are received in 96 per cent alcohol and stained in a watch glass. The stain is to be heated over the spirit flame until small bubbles arise which make a crackling noise (65° to 70° C.); sections are then transferred to aniline-oil-alcohol until differentiated. The process of differentiation is ended when no more coarse clouds of color go off into the fluid. The section is then transferred to the slide, dried with filter paper, after which some drops of oil of cajeput are applied, and the sections are again blotted with filter paper. A few drops of benzene are poured on the sections, blotted again, and finally some benzene-colophonium added, a cover glass placed over the section, and the slide heated until all the benzene gas has been driven off. Upon cooling, the section is thus permanently mounted.

The stain is made as follows: Methylene blue, B. pat., 3.75 grams; Venetian soap, 1.75 grams; distilled water or soft water, 1,000 c. c. The differentiating or decolorizing fluid has the following composition: Aniline oil, colorless, 10 parts; alcohol, 96 per cent, ninety parts. Nissl obtains his aniline oil directly from the factory at Hochst and keeps it carefully protected from the light. The benzene-colophonium is prepared by pouring benzene upon colophonium (white rosin) and alowing it to stand for from twenty-four to thirty hours. This results in a fluid transparent mass which can be brought to the desired thickness either by the addition of more benzene or by allowing it to evaporate, and then it is ready for use. In mounting, while driving off the benzene gas by heating over the flame, the material may catch fire, but if the flames are blown out immediately no injury is done, and the alterations produced by the burning are quite characteristic and easily recognizable. The above description has been given in detail as it is the classical method, which, as above and with various modifications to be described later, has been used by the writer in this article. This method distinguishes within the cell-body always two and sometimes three constituents. One of these constituents of the protoplasm stains entirely blue by this method, and is spoken of by Nissl as the stainable or visible formed part of the nerve cell. The second part remains entirely unstained, and is spoken of by him as the unstainable or the visible unformed part of the nerve cell-body. In addition to the above, in many nerve cells, pigmentary deposits are visible which have been especially studied recently by Rosin (1896). Nissl has prepared a somewhat elaborate classification of cells according to the character and arrangement of the stainable portion to the non-stainable portion of the cell-body in different cells in different parts of the central nervous system. This stainable substance shows a series of different forms; smaller and larger granules of regular or irregular shape, arranged in groups or rows. These stainable masses are sometimes arranged in threads, smooth or rough, and varying in thickness, course, and length. Often larger structures, regularly or irregularly shaped, are seen, which stain with varying degrees of intensity, some appearing homogeneous, others showing a complex internal construction difficult to describe.

Three varieties of these larger bodies are especially to be noted, (1) the so-called "nuclear caps" (Kernkappen), stainable masses in the form of regular or irregular cones hollowed out like a cap and corresponding to one pole of the nucleus upon which it rests. There may be two such caps within one cell-body at opposite poles, and occasionally, according to Nissl, three such caps may exist within a single cell. (2) So-called "wedges of division" (Verzweigungs-Kegeln), stainable masses completely filling the angle at the point of division of a nerve cell process.

(3) Spindles, oblong spindle-shaped stainable bodies, thick in the middle and thinner at both ends, the latter sometimes tapering off into thread-like filaments. These spindles may be one or two-sided. Any one of these forms may be vacuolated. Nissl makes a rather elaborate classification of these ganglion cells according to their internal morphology, after spending years in the most exact investigations of various nerve cells in the different nerve centers of man and animals. He has come to the conclusion that definite types or variations of nerve cells exist which are constant not only in the same animal but often exist characteristically in homologous localities in a whole series of animals. According to him, all the cells in the nerve centers, except the so-called chromophile nerve cells, can be divided into two main classes. The first class includes the nerve cells which possess a well marked cell-body surrounding the nucleus completely on all sides, the protoplasm having a distinct contour. These are called somatochrome nerve cells. The second class (sub-divided into two groups, cytochrome and caryochrome) includes those cells in which, in Nissl preparations, the nucleus is most in evidence, the nucleus has a clear contour, but only indications of a cell-body are present, an appearance due to either the scanty development of the cell-body or to the predominance in it of the unstainable substance.

These cells often look as if they were naked nuclei, though by Golgi's method it can be shown that they may possess definite axones and dendrites. In some of these cells the stainable substance may be present, but very unevenly distributed, at different points in the cell, the nucleus appearing as if only partially surrounded by protoplasm. Nissl classifies these cells with such an ill-defined cell-body, the nucleus appearing only partially surrounded and not exceeding in size the nucleus of a neuroglia cell or of an ordinary leucocyte, as "granules" (Körner) or cytochrome nerve cells. These cells are present in great numbers in the granular layer of the cerebellum, also in the cerebral cortex and the olfactory bulb—being different varieties and not identical. The second subgroup of cells, in which the cell-body is only indicated but the nucleus is of the size of an ordinary nerve cell, or at least larger than that of a neuroglia cell, he designates as caryochrome nerve cells. There are varieties of these as in the substantia gelatinosa Rolando, and those of the ganglion habenula—these types being designated at present by letters of the Greek alphabet. A majority of the nerve cells fall in the first group—the somatochrome cells—where the cell-body, in the light of morphology, has apparently greater relative importance than the nucleus. In this group are a series of types of nerve cells to be distinguished from one another partly through differences in the nuclei, but chiefly through different relations of the stainable and unstainable constituents of the cell-body.

These somatochrome cells were originally divided by Nissl into four groups, but now he includes them all in three groups as follows:

Group I. Arkyochrome nerve cells—stainable portions of cell-body in Nissl preparations in the form of a network, branches of which appear to be distinctly connected. Nissl notes, however, that in many of these cells processes can be made out into which the distinct network of the perinuclear part of the cell-body can go over, thus forming a parallel-striped arrangement. These arkyochrome cells Nissl subdivides into enarkyochrome forms and ampharkyochrome forms. The former shows the stained constituents arranged in the form of a network, which differs from the latter in that the intensely stained radiating nodal points of the network are connected in the cell-body by deeply stained thick bridges so that a further connected network of very deeply stainable substances is observable. Both these sub-groups of cells are widely distributed throughout the central nervous system. The former have been observed by Nissl in the spinal cord, but are most numerous in the large dorsal nucleus at the proximal end of the medulla. What he formerly classified as Group III, arkyostichochrome nerve cells, are now included in this first group (1897a). He describes these cells as presenting a striated appearance with a network-like structure united in a most intricate manner.

The Purkinje cells of the cerebellar cortex were given as typical examples of cells of this sort. (See Plate IX, Fig. 27).

Group II. Stichochrome nerve cells, stainable substance arranged in striæ, running in same direction, and usually parallel to contour of cell-body, in part also with surface of nucleus. These striæ, made up of different stained elements, threads, spindles and granules, are more or less isolated and in rows. Nissl describes four types of these cells represented by (1) nerve cells of motor nuclei, (2) large cells of cornu Ammonis, (3) certain cells of cerebral cortex, and (4) certain cells of spinal ganglia.

Group III. Gryochrome nerve cells, stainable substance entirely made up of small granules distributed in threads or heaps. Nissl does not give an illustration of these cells, but states that they are to be found particularly but not exclusively in the corpus striatum. Nissl states further that transitional forms exist which are difficult to definitely classify, but that the cells of a wholly definite structure are situated throughout the animal series in homologous localities. He has also shown that all these types of cells may, under certain circumstances, show different staining relations (1894a), that is, the individual members of a certain group of cells belonging to one type may be palely, moderately, or intensely stained. This difference seems to depend upon the concentration of the stainable substance in the cell-body. The darkly stained cells he designates as pyknomorphous cells, in which stainable portions are arranged relatively most closely; intermediate stages are designated as parapyknomorphous cells; while very feebly stained cells are designated as apyknomorphous, in which stainable masses are not arranged close to one another but are somewhat widely separated by the non-stainable constituents of the cell-body. Nissl furthermore mentions that often the nucleus shows modifications which correspond in greater or less degree to the staining intensity of the cell-body, so that in an apyknomorphous cell the unstained nuclear substance is relatively more abundant than in the pyknomorphous cells. This holds in the somatochrome cells, and to a less degree in the caryochrome and cytochrome cells.

Supposed to be more or less in the nature of an artefact are the so-called chromophile nerve cells which one finds often single or in small groups along with the other nerve cells, but in which the stainable substance seems to be evenly diffused throughout the cell-body, making it impossible to distinguish a stainable from an unstainable constituent in the cell. Nissl (1896c) states that they are always relatively smaller than pyknomorphous cells. The explanation of these forms is not as yet entirely satisfactory, but they are supposed to be due to the action of the reagents employed, though under certain circumstances they may have a pathological significance. Another nomenclature has been introduced by Flesch (1897), in which he speaks of chromophilic cells and chromophobic cells with transitional forms, and attributes the differences to variations in the internal chemistry of the cells, this latter depending in part upon differences in the devolopment, in part upon differences in metabolism or function.

Von Lenhossek (1895) gives a very accurate description of the appearances within the cells of the ventral horn of the spinal cord and in the cells of the spinal ganglia. He has found that thionin stains as well if not better than methylene blue, and Barker (1899) has obtained similar results, but states that crystalline deposits have been more frequent in preparations stained with thionin than in those stained with methylene blue. In material hardened in Lang's solution or other corrosive sublimate solutions, the writer has at times detected crystalline deposits, whether stained with thionin, methylene blue or methylene violet, and attributed the same to the fixative fluid and not to the stain at all, as no crystalline deposits have been observed with other fixative agents—alcohol, formalin, and Van Gehuchten's fluid—regardless of which stain was used.

It would be interesting to know whether corrosive sublimate fixation was used by Barker in the above mentioned preparations. Van Gieson uses polychrome to a considerable extent as a stain, but it seems to the writer to give a paler and less distinct stain than either methylene blue or methylene violet, and has a tendency to fade after a time. Referring to von Lenhossek again, he objects to the term "granules" for the stainable substance, the masses being ordinarily much too coarse to be so designated. He has given accurate descriptions of their characteristics and arrangement in various animal species. This stainable substance of Nissl he designates as "chromophile corpuscles," and later uses the term "tigroid masses" (1896).

De Quervain (1893) has suggested that the chromophilic bodies or corpuscles are aggregations of fine granules, but von Lenhossek refuses to admit that all such bodies represent aggregations of minute granules. Schaffer (1893) first described the peculiar behavior of the axone and adjacent portion of the cell-body known as the axone hillock as regards Nissl staining, this space being entirely free from this stainable substance of Nissl. With Kronthal's method the axone and axone hillock stain intensely in methylene blue, but Benda (1895) found that when specimens thus prepared were cleared in creosote this region lost its color and only the stainable substance of Nissl in the cell-body and dentrites retained its color. He found one exception, however. In the basal axones of the pyramidal cells of the cerebrum, especially of those known as the giant pyramidal cells of Betz, just at the beginning where a collateral is coming off at right angles, a small wedge-shaped granule, triangular in section, takes up the methylene blue, the axone itself not staining at all. These different results obtained by differences in technique emphasize the writer's previous statement of the necessity of a full knowledge of the history of the case and every detail of technique before coming to any conclusions in a given case.

With this brief review of the more important literature on the internal structure of the nerve cell we will now turn to the arrangement of the cells in the cortex. To go into the literature of this subject in detail would be sufficient material for an article in itself, so that it will be passed over as briefly as possible. Table I shows the arrangement of the cells as described by the more important contributors to this subject. As early as 1782 Gennari divided the cortex at the posterior pole of the cerebrum into three layers, an external and internal gray layer separated by a white layer (so-called line or band), the "line of Gennari." Vicq d'Azyr, in 1786, described this region as also made up of an inner and outer gray layer between which was a white layer (line or band), the "line of Vicq d'Azyr." Meckel, in 1812, stated that the gray layer of the cortex is single in all parts but the occipital region and cornu Ammonis. In the occipital region a band of white substance, the line of Vicq d'Azyr, separates the gray substance into an external and internal gray layer, so that the structure of this part of the brain is more complex than the rest of the external cortical region. Coming down to 1840 Baillarger first examined the cortex carefully, and described three gray and three white layers, or six layers in all, alternating gray and white. From his descriptions the line of Gennari or Vicq d'Azyr, in the occipital region, received the additional name of the "line of Baillarger." In 1841 Remak examined the cortex microscopically as well as macroscopically, but without the use of staining agents, and described a four-layered type made up of two gray and two white layers alternating with one another.

Somewhat later (1852) Kölliker described a three-layered plan, the inner layer appearing of a yellowish red color, the middle of a grayish color, and the outer of a whitish color.

Berlin, in 1858, first used stains in his work, hardening pieces of the cortex in chrome salt and staining with carmine. He described six layers as the type, the upper five from the character and arrangement of the cells and the lower as a layer free from cells. He describes the layers from within outwards toward the surface, reversing the usual order of all other authors, and leading to considerable confusion, unless this fact is carefully noted. Clarke, in 1863, described eight layers as the common type, and Luys the following year, 1864, described just one half that number, or four layers, as the common type. Arndt, in 1867, described a five-layered type, and Meynert in the same year divided the cortex into a motor and a sensory region, the former anterior to the fissure of Rolando, and the latter posterior to the same. He described five layers as the common type, and eight layers as the type in the occipital region. Cleland, in 1870, described rather a complex arrangement of the cortex into a four-layered type, the third layer being separated from the fourth by what he designated as the "primary pale band." The "deep pale band" is included in and forms the lower part of the fourth layer. Henle in the same year described a four-layered type made up of (1) the outer layer, (2) outer spherical cell layer, (3) pyramidal cell layer, and (4) inner spherical cell layer. Charcot, the following year, 1871, described the layers of the cortex as five in number, (1) superficial layer, (2) small pyramidal cell layer, (3) larger pyramidal cell layer, (4) granular cell layer, and (5) fusiform cell layer; approximating that used by many of the subsequent authors. Lewis, in 1876, described five layers as the type for the motor area and six layers as the type for the sensory area. Major in the same year, 1876, described six layers as the common type, and Krause, also in the same year, described seven layers as the common type. Betz, in 1881, made the division into five layers as the type for the motor area, but divided the sensory region into eight layers as the type—a classification somewhat similar to Meynert's, but with a different nomenclature.

Golgi, in 1883, using his impregnation method, divided the cortex into three layers as the type, (1) superficial or small pyramidal cell layer, (2) middle or larger pyramidal cell layer, and (3) internal or irregular cell layer. Schwalbe, in 1885, described a curious arrangement of the cortex into four layers, the upper two known as the "outer Hauptzone" or chief zone, and separated from the lower into two layers, known as the "inner Hauptzone" or chief zone by the "boundary zone" or "line of Baillarger." Obersteiner's (1887) division into a five-layered type is similar, except as to the nomenclature, to that of Charcot's common type, Lewis' motor type, and Betz's motor type. Cajal, in 1890, recognized the same three layers as Golgi in the common type, but added a fourth layer, which he called the first or molecular zone, then followed the second, or zone of small pyramidal cells; the third, or zone of large pyramidal cells, and the fourth, or zone of polymorphous cells; thus making four layers in all. Golgi's first layer is thus seen to include the first and second layers of Cajal. In the occipital lobe, Cajal describes an additional layer of vertical fusiform cells between the first or molecular layer and the layer of small pyramidal cells, the other layers being similar to his common type, and thus making five layers in this region. Gowers, in 1893, adopted practically the same division into a five-layered motor type and six-layered sensory type as described by Bevan Lewis in 1876. Hammarberg, in 1895, described six layers as the type, with numerous variations in different parts of the cortex. Edinger, in 1896, describes four layers, similar to Cajal as the type, and Starr (1896), in his atlas of nerve cells, also describes a similar arrangement. Nissl (1898) describes a four-layered type as follows: First, or layer poor in cells; second, or layer of pyramidal cells containing 2 equals layer of small pyramidal cells (equals 2 of Meynert's layers) plus 3 equals layer of larger pyramidal cells (equals 3 of Meynert's layers); third, or layer of small cells (equals 4 of Meynert's layers); and fourth, or internal (6) plus external (5) zone of the layer of medullated fibers (equals 5 of Meynert's layers). Region 5 equals ganglion cell layer, and region 6 equals spindle cell layer of Hammarburg. It will be seen that there is much variation and not a little confusion in adjusting these various arrangements and classifications to one another, and in order to simplify the matter as much as possible the writer suggests that as the large and small pyramidal cells are so intermingled and merged into one another, they should be included in one layer, thus making three layers the common type, as follows: First, or superficial layer, corresponding to the first layer of Cajal and Edinger; second, or pyramidal cell layer, corresponding to the second and third layers of Cajal and Edinger; and third, or spindle cell layer, similar to the fourth layer of Cajal and Edinger. This arrangement differs from Golgi's three-layered type in that the latter recognized no superficial or tangential fiber layer, but includes this as the upper part of his first, or layer of small pyramidal cells, whereas in the writer's arrangement one pyramidal cell layer includes both the large and small pyramidal cell layers of Golgi. The third layer of Golgi and of the writer are the same as the fourth layer of Cajal and Edinger. This classification into three layers as the type will be used for convenience in the subsequent description of the plates. That there are variations from the type in different parts of the cortex, of course, is recognized by all who have worked in this field to any extent, and, furthermore, specialized parts of the cortex have a specialized arrangement, as the cornu Ammonis, for example.

In turning now to the pathological investigations by means of the Nissl stain (1898), they are found to have been exhaustive and varied, including most parts of the central nervous system in both man and animals and in many forms of disease. A brief review only will be given of the contributions containing descriptions of researches by Nissl's stain in that form of mental derangement known as dementia paralytica, or general paresis. Nagy (1894) carried on his investigations by means of the Nissl stain, and found the greatest changes in dementia paralytica, including various stages of cell degeneration up to complete destruction of the same—the cells most altered being those of the frontal lobes, and least changed those of the occipital lobes. Changes of a high grade were also shown in the cells of cases dying after severe epileptic insanity—here the gyrus rectus and cornu Ammonis being affected the most. In chronic forms of insanity similar changes were found, but the number of cells entirely destroyed was undoubtedly smaller than in the above mentioned forms of illness. In acute hallucinatory confusional insanity only the beginning stages of alteration were found; similarly in mania. He finally states that each form of mental derangement showed the highest grade of change in which the clinical picture of the worst suffering was present, while in the curable forms there were found corresponding slight changes. Belmondo (1896) employed the Nissl method in investigating the alterations in the nerve cells in dementia paralytica, and did not find changes of great gravity—at most the cell protoplasm being much diminished and disintegrated; now and then pigmentary atrophy, as much in the Rolandic region as the frontal lobe, is found, and in other parts a diffuse chromatolysis is to be seen. He condemns the expression meningo-peri-encephalitis, which implies a conception of an inflammatory process.

Boedecker and Juliusburger (1897) examined sections of cortex from the central and parietal convolutions of three cases of dementia paralytica by the Nissl method. They found thickening of the pia with septa projecting into the cortex, containing blood vessels whose walls showed no special thickening but were surrounded by rich deposits of pigment granules, which latter were also found here and there, distant from the septa in the cortical network. In regions most affected the cortex did not present its well known layering. There was to be seen a thicklycompressed granular crowding with different shaped granules; thin, spindle-shaped, round, or oval, with strongly colored ones lying adjacent to those only slightly colored. There was increase of blood vessels and hypertrophy of the interstitial network, with corresponding decrease in the number and size of the cells. Many cells were considerably diminished in size, markedly shrunken, entirely without processes, and intensely colored. At times a differentiation into nucleus and granular cell-body was not possible, owing to complete chromatolysis, and very seldom were cells found with a strongly colored nucleus, strongly colored fine granules about the same, with larger granules at the periphery of the cell-body—a partial chromatolysis.

By the Marchi method these investigators determined a degeneration of the fibers from these cells extending into the spinal cord. They conclude the process to be an intense degeneration and proliferating one, going on hand in hand—degeneration of the cells and proliferation of the interstitial network, with increase of blood vessels. Crisafulli (1897) notes a great variety of changes in dementia paralytica. The cellular changes are most advanced and diffuse in the frontal lobes, but are not limited to that region. He examined sections from the frontal, parietal, occipital and temporo-sphenoidal lobes of both hemispheres. He found pallor, granular disintegration, and loss of chromatic substance. Often the cell-bodies were atrophied or contained an excess of yellowish pigment, and their numbers were reduced. The nuclei were often eccentric, and all stages of the destruction of the nucleus were observed. While the alterations shown by Nissl's method were not less constant than those demonstratable by other methods, Crisafulli does not consider them characteristic of the disease or in any way different from those seen in some other mental diseases. They are, however, more or less grave and diffuse and not limited to a single cortical center; with varying degrees of degeneration of the nerve cells. He further states that, provided the nerve cell element degeneration is not greatly advanced, it is impossible to find any alteration of the blood vessels, and, finally, that when the psychosomatic condition of the paralytic is not greatly aggravated and death intervenes from other causes, it is possible that the pathological report will note some elements which are not degenerated, although there may be various alterations. His article is illustrated by eight figures showing cells in various conditions of degeneration.

Angladi (1898) reports a case of acute dementia paralytica in which death occurred after a series of epileptiform convulsions when the patient was at the age of thirty-seven years. The autopsy showed peri-encephalitis. Preparations were made from the ascending frontal convolutions and the anterior part of the frontal lobe of the left hemisphere. He states that not a single one of the pyramidal cells preserved its normal characteristics, and the transformation in the great majority of cases semed to be various stages of the same process—various stages of chromatolysis, vacuolization, eccentricity of the nucleus up to rupture of the cell wall and extrusion of the nucleus and, finally, complete destruction and disappearance of the cell. The chromatic substance is first attacked, and some few cells relatively healthy showed about the nucleus the first stages of dissolution. Destruction of the achromatic network was shown by formation of vacuoles at the periphery of the cell, increasing gradually up to complete destruction of the substance of the cell. The nucleolus becomes vacuolated and disappears. The nucleus is attacked by central chromatolysis and disappears *in situ*, or becomes eccentric, or the cell-body may rupture and the nucleus be extruded, becoming irregular, compressed or shriveled. The contour of the cells is always irregular, and the prolongations either broken or tortuous. He states that the cells of the medulla and cord show identical alterations. Angladi finally concludes by stating that we do not know whether these lesions are the cause or the result of the malady, and asks the question, "Are the lesions primary or secondary to an alteration of the vessels or interstitial tissue?"

Berger (1898) examined the anterior horn cells of the spinal cord in twelve cases of dementia paralytica and found lesions affecting principally the chromatic substance in 83 per cent of the cases. He failed to find a strict parallel between these cellular lesions and those of the fibers and cortex, or between them and the clinical symptoms of the disease. He illustrates his article by figures of these cells.

Nissl (96a), in 1896, stated that he maintains the same position as Kraepelin, namely, that one sees in dementia paralytica a general disease with the histopathology directed especially to the cortex. The pathological changes in the blood vessels are obscure, and the relation of the glia to the blood vessels is complicated, also the condition of the lymphatic vessels. Some authors regard the disease as an inflammatory process, others that a chronic interstitial inflammation enters into it, others that it is a parenchymatous process, and still others that it is a histopathological process in which the specific tissue is diseased primarily. Nissl notes that an inflammation without the blood vessels sharing in it cannot be thought of. He states that the appearance of the paralytic cortical disease can be present without the blood vessels being diseased and without the blood vessels containing any elements of an inflammatory process. Also there may be a high grade of disease of the tissue (Gewebe) in excess of any disease of the blood vessels, and only a slight involvement of the tissue, and *vice versa*, a severe tissue damage with only insignificant disease of the blood vessels. Also direct inflammatory blood vessel changes with infiltration of the walls of the same with leucocytes and "mastzellen," which may rarely pass out into the adjacent regions. In some cases this inflammatory alteration of blood vessels results in a massive production of decay of numerous neurones. These inflammatory changes in the blood vessels have nothing directly to do with the chief paralytic process, and are only found in the cortex when sepsis-producing bacteria are present. It therefore follows that the paralytic cortical disease can be regarded either as the result of disease of the blood vessels or as an inflammatory process. Almost all cases of dementia paralytica show a slight or severe disease of the blood vessels. There may be also a leptomeningitis, disease of the beginning part of the aorta, an injury to the diplœ, brittleness of the bones, or there may be a general arterio-sclerosis. If it is not a disease of the arteries or an inflammatory process, it may be a primary disease of the glia or of the cortical neurone. Changes in glia are progressive in kind (mitosis of glia nuclei, hypertrophy of glia cells, and increase of glia fibers) with regressive changes in the cortical neurone—an acceptation that results of investigation directly contradict, since we find in the most luxuriant increase of glia that the nerve cells are only slightly or not at all changed, and *vice versa,* in the most severe nerve cell changes the increase of glia may be only slight. The acceptation of a primary glia fiber increase is absurd, since the glia fibers are an intercellular substance. Nissl therefore concludes that the cortical disease of dementia paralytica is a primary disease of the cortical neurone; at the same time with the regressive changes in the cortical neurone goes the progressive changes in the glia cells. Histopathological investigations of paralytic cortical disease has to deal chiefly with the following difficulties: (1) a paralytic diseased cortex and the, to us, available cortex of the dead paralytic are two different things. Entire series of original circumstances that damage the neurones of the cortex without having anything to do directly with the paralytic process is to be noted, as the complete closure of a blood vessel which only indirectly bears upon the original process. Also death of a paretic from typhus fever, septic pyemia, etc. The problem is extremely difficult, as there is no specific disease of the cortical cells, and, furthermore, there is no paralytic cortical cell disease, although there is a paralytic cortical disease. The kind of disease of the cortical tissue is worthy of being pointed out. (2) It is not sufficient to know that the cortical neurone is diseased, but it is important to know which cortical neurones are damaged. Attention to the kinds of nerve cells directly diseased is important for the real conception of the disease process, and also for the critical examination of the plan of the cortex and its functions. Nissl differentiates the following forms of disease of the cells of the cortex in dementia paralytica: (1) Acute progressive disease. In certain cases the disease ends with the complete destruction of the elements of the cortex. (2) The chronic disease progresses slowly, resulting in either a pigmentary degeneration or in a decay of the cell-body and nucleus, and ends with so-called cell sclerosis. (3) The severe disease of the cortex which runs either an acute or subacute course and terminates with the death of the cell. The necrotic cells persist commonly either bleached out or having the appearance of colliquation or of vaucolization of the ground work. (4) The combined form of the disease, in which the cell may be acutely diseased without either a cure following, or, on the other hand, the ordinary course being taken that terminates with the destruction of the cell. Midway in its course the disease process is arrested and takes on the symptoms of the chronic disease. The severe cortical cell disease is entirely overlooked by former authors. It differs in that the nucleus is also involved and a process of liquefaction takes place in the same. It becomes smaller, shrunken, the contours become homogeneous and tinged, the nucleolus sinks to the nuclear wall, which latter is irregular and shriveled into folds, the network cannot be distinguished, and vacuoles and crystals may be formed. In the necrotic cells calcareous deposits may be found, as is seen in other cortical cell diseases, as sclerotic elements. These chalky or calcareous concretions occur in the form of fine granules, crumbs, placques, or stalactitic masses, which are intensely colored with methylene blue. The entire cell may be bleached or only a single part, as some of the fine dendrites or only a single dendritic process, or only the nucleus, or, finally, only the nucleur membrane. This calcification, moreover, is an exceedingly important phenomena, since we are entitled to conclude that partially calcified cells are no longer functionally active and are necrotic. Under similar conditions in acute diseases we recognize the phenomenon of death in the affected cells. If one places the preparations in alcohol after twelve hours postmortem, any mistake in this direction may be obviated. Whoever grasps the histopathology of the cortical cells will guard against any mistake in regard to the above mentioned death phenomena. Ewing, in 1898, used the Nissl method in observations upon the changes found in ganglion cells of the central nervous system in various pathological conditions, and stated that various grades of chromatolysis were found in the cortical cells in dementia paralytica.

Ballet (1898) exhibited sections from the paracentral lobule of both a normal and a paretic brain, stained by the Nissl method.

In the normal brain, under a magnification of forty-five diameters, the four layers of Schwalbe and Ramon y Cajal were easily discoverable, but in the paretic sections, in marked contrast, they were recognized with difficulty; also in the latter, great numbers of capillaries were noted in the third layer and white subcortical substance, the nerve cells were less numerous, and in all cases less distinct and lost in the midst of a mass of nuclei. At 130 diameters the contrast was still more marked, and at 250 diameters vascular lesions were noted consisting of enormous dilatation of the capillaries and arterioles, the investment of these vessels by a casing of lymphatic corpuscles which distended the adventitious sheaths, and the accumulation of pigment at certain points, particularly in the neighborhood of the bifurcations. These alterations are also revealed by hematoxylin and picro-carmine, and have been described for a long time by all observers, but the Nissl method shows the changes more clearly than any of the others.

In addition to these changes one may mention the multiplication of the white corpuscles and their migration from the vessels by diapedesis, as due in part perhaps to the proliferation of cellular elements of the neuroglia which accumulate in the interstitial tissue, principally in the neighborhood of the vessels or about the nerve cells. At 600 diameters one easily distinguishes the small white cells (lymphocytes), with small nuclei deeply colored and with but a small amount of protoplasm; large white globules with protoplasm somewhat abundant and with voluminous nuclei irregular in form and less impregnated than those of the lymphocytes by the methylene blue; and, finally, polynuclear leucocytes. But interest in Nissl's method is chiefly in the study of the lesions of the nerve cells. At 600 diameters one sees the profound alterations undergone by these cells. In examining the elements of the third layer (large pyramidal cells) or the giant cells of Betz, there is a tendency in them to lose their triangular shape and become oval or rounded, the protoplasmic prolongations are atrophied and but slightly visible, the chromophilic granules for the most part undergo a process of disintegration and are reduced to a sort of fine powder or dust, or are entirely dissolved in the mass of protoplasm. The author then discusses the nature of the process, some authors (Magnan, Mierzijewski, Mendel) claiming the primary disease to be that of the neuroglia framework—an interstitial encephalitis. Others on the contrary (Tuezeck, Ziegler, Binswanger, Joffroy, Pierret) claim it affects primarily the nervous tissue, either the nerve fibers or the nerve cells; thus being a parenchymatous encephalitis. The more Ballet studies the pathological anatomy of dementia paralytica the more he is convinced that the first and most important lesions are those of the blood vessels. These are seen in every case, while those of the cells are inconstant, variable in degree, and subordinated to those of the vessels. This is not to say that the cellular alterations may be, as some authors claim, the result of the mechanical choking of the cells by the proliferating interstitial tissue which makes their pathology more complex, but he thinks the result is due less to the compression by the thickened neuroglia than to the difficulties of assimilation, owing to either the circulatory obstruction or the action of the toxines carried by the blood. Ballet then discusses the relation of syphilis to dementia paralytica, and states that the pathological anatomical findings in the two cases are practically identical, and advocates a syphilitic etiology for the disease.

In this historical review of the literature on the pathological conditions found in dementia paralytica by the employment of the Nissl method, it is to be noted that but few of the contributions were accompanied by figures illustrating the various pathological findings described in the text.

(*To be continued.*)